Evidence-based Practice Center Systematic Review Protocol

Project Title: *The Effect of Dietary Digestible Carbohydrate Intake on Risk of Type 2 Diabetes, Growth, Size, and Body Composition*

I. Background and Objectives for the Systematic Review

The Dietary Reference Intake (DRI) for carbohydrates was last released in 2005[1] and in the decades since, interest and available data in this field have grown tremendously. Understanding whether and when carbohydrate intake is a modifiable risk factor for disease or poor health can inform primary and secondary prevention strategies and subsequently improve population health.

DRI for carbohydrates can be linked to chronic diseases such as diabetes and obesity, which affect the lives of millions of people in the United States and globally. Since these disease states become more prevalent with age, they are likely caused by a cumulative exposure to external factors such as nutrient intake combined with a particular genetic predisposition.

Carbohydrates are organic compounds that are made up of molecules of carbon, hydrogen, and oxygen, which are absorbed as monosaccharides (e.g., glucose) before they can be used as energy for human cellular function. As such, their pathophysiological role in type 2 diabetes (T2D) and other forms of glucose intolerance has been of interest for a long time. Longitudinal nutritional studies show that higher intake of high-quality carbohydrates, in addition to other lifestyle factors, can lead to a 90% risk reduction in the development of T2D compared with individuals who do not adhere to these dietary patterns.[2, 3] In contrast, low-quality carbohydrate consumption, which includes the consumption of ultra-processed foods, is associated with a higher risk of developing T2D, even after adjustment for body mass index (BMI).[4, 5] These studies exemplify an important principle of carbohydrate consumption that is "quality over quantity." In addition, the role of very low carbohydrate or ketogenic-style diets in the prevention of T2D has also been studied with mixed results due to different definitions of "low carbohydrate" and heterogeneous study designs.[6] These studies were criticized for inadequate adjustment of confounding, such as weight loss, and higher fat consumption, which often accompanies dietary changes. Outcomes of ketogenic diets may inform a new DRI for carbohydrates.

T2D is a heterogenous condition with a polygenic basis, and defects in insulin secretion and insulin action are at the core of T2D pathophysiology. Genetic susceptibility can influence the trajectory of progression from impaired glucose metabolism to overt hyperglycemia. For example, certain gene variants of *TCF7L2*, which is associated with T2D in populations with diverse genetic origins, are associated with dysregulated beta and alpha cell function and contribute to the development of T2D.[7] There are additionally variations in racial and ethnic susceptibility to T2D, which are associated with carbohydrate consumption.[8] It is unknown if chronic carbohydrate consumption in populations with *TCF7L2* polymorphisms or other types of genetic susceptibility influences the rate of progression towards T2D.

The biggest risk factor of the development of T2D is obesity, defined as an abnormal or excessive fat accumulation that presents a risk to health. The treatment of obesity involves creating an energy deficit between energy intake (calories consumed) and energy expenditure

(calories expended). Although some have proposed that the type of calorie consumed (in this case calories of carbohydrate origin) may influence energy partitioning, this is still not widely accepted to be true.[9, 10] Hence, an important question to answer is whether carbohydrate consumption influences body weight regulation and body composition, independent of its calorie content.

In infants and children, carbohydrate intake is critical for growth and development. Glucose is the main oxidative fuel of brain cells and carbohydrate intake is linked to cognition.[11] Carbohydrate intake influences metabolism and can minimize the protein cost of gluconeogenesis and irreversible protein and nitrogen loss, and carbohydrate intake prevents ketosis and its consequences, affecting growth. Population-based studies in children link carbohydrate intake and its subtypes, such as monosaccharides and disaccharides, with changes in serum lipids.[12] Furthermore, some evidence exists associating sugar-rich (particularly fructose rich) diet with increased risk for nonalcoholic fatty liver disease (NAFLD) in children who have obesity.[13, 14] Unfortunately, most studies about carbohydrates intake and energy metabolism have been conducted in adults and newborns, the latter being in a transitional phase of metabolic adaptation. Thus, studies performed in children between one year and puberty are likely sparse.[15]

Purpose of the Review
This systematic review and meta-analysis will evaluate the Key Question (KQ) listed below. This review intends to summarize and appraise all relevant evidence to inform the upcoming U.S. and Canadian government DRI guideline about carbohydrate intake.

II. Key Questions (KQ)

KQ 1: What is the association between dietary digestible carbohydrate intake and the incidence of type 2 diabetes (T2D) and effect on growth, size, and body composition (i.e., obesity, overweight, body weight and composition)?

Please see Table 1 for inclusion and exclusion criteria by Population, Intervention, Comparator, Outcome, Timing, Setting/Study Design (PICOTS)

III. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

We will apply the following inclusion and exclusion criteria for the studies identified in the literature search (Table 1).

Table 1. Inclusion and Exclusion Criteria by Population, Intervention, Comparator, Outcome, Timing, Setting/Study Design (PICOTS)

PICOTS Elements	Inclusion Criteria	Exclusion Criteria

Population	• Participants who are generally healthy, including participants who are determined to be overweight/obese, women who are pregnant or lactating
	• Age of participants
	  ○ Between 2 and 9 years (before puberty)
	  ○ Between 9 and 17 years
	  ○ 18 years and older
		• Studies that enroll participants with diseases/health-related conditions that impact carbohydrate absorption or metabolism including cancer and malabsorption syndromes
		• Studies that exclusively enroll participants hospitalized with an illness or injury
		• Studies that exclusively enroll participants with type 1 or 2 diabetes (i.e., studies that aim to treat participants who have already been diagnosed with the endpoint outcomes of interest)
		• Studies designed to induce weight loss or treat patients who are determined to be overweight and obese through energy restriction or hypocaloric diets for the purposes of treating additional or other medical conditions
		• Studies that exclusively enroll participants who are determined to be undernourished, underweight, stunted, or wasted
		• Studies that enroll participants who are prebariatric or postbariatric surgery
		• Exclude participants less than 2 years old

Interventions	• Total dietary digestible carbohydrate intake from foods, beverages, and dietary supplements ○ Total dietary digestible carbohydrate intake defined as collective starch and sugar intake; carbohydrate intake not including dietary fiber) • A dietary pattern that quantifies the intake of total dietary digestible carbohydrates and allows the isolation of the effect of carbohydrate intake from the effect of the intake of other macronutrients	• Studies that do not specify the amount of total digestible carbohydrate intake (e.g., studies that only report type or source of digestible carbohydrate) • Studies that do not describe the entire macronutrient distribution of the diet (i.e., studies that do not report total digestible carbohydrate, total fat, and total protein contents of experimental or baseline diets) • Studies that only assess digestible carbohydrate intake via infusions (rather than the GI tract) • Studies that primarily measure postprandial responses, as opposed to longer term studies • Studies that examine food products or dietary supplements not widely available to U.S. consumers • Multi-component interventions that do not isolate the effect or association of digestible carbohydrate

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Comparators	• Different total dietary digestible carbohydrate intake level(s)	• Comparison of different sources of carbohydrates without specifying the amount of carbohydrate intake • Studies that do not attempt to control for the energy intake of participants such that comparisons are made on an isocaloric basis. • Comparisons of available carbohydrate exposure should not be confounded by differences in participants' energy intake.

Outcomes	• Incidence of type 2 diabetes
	• Incidence of gestational diabetes
	• Surrogate markers suggesting prediabetes or abnormal glycemia
	  ○ HbA_{1C} level
	  ○ Glucose tolerance/insulin resistance/insulin sensitivity
	• Growth, size, and body composition
	  ○ Body weight
	  ○ BMI
	  ○ Body circumference
	  ○ Body composition and distribution
	  ○ Classifications of underweight, healthy weight, overweight, and obesity
		• Type 1 Diabetes

Timing	• Type 2 diabetes • Minimum intervention length of 12 weeks Effect on growth, size, and body composition ○ Minimum intervention length of 12 weeks	• Any intervention length <12 weeks
Settings	• All except hospital and acute care	• Hospital and acute care
Study design	• Randomized controlled trials • Nonrandomized controlled trials, including quasi-experimental and controlled before-and-after studies • Prospective cohort studies • Nested case-control studies • Relevant systematic reviews, or meta-analyses (used for identifying additional studies)	• In vitro studies, nonoriginal data (e.g., narrative reviews, scoping reviews, editorials, letters, or erratum), retrospective cohort studies, case series, qualitative studies, cost-benefit analysis, cross-sectional (i.e., nonlongitudinal) studies, survey
Publications	• Studies published in English only • Studies published in peer-reviewed journals • Studies published at and after the year 2000	• Non-English language studies

Abbreviations: BMI = body mass index; HbA_{1c} = hemoglobin A_{1C}; GI = gastrointestinal; KQ = Key Question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial; U.S. = United States

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

We plan to conduct a comprehensive database search, including Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from database inception to the present. We have developed a preliminary database

search strategy (Appendix A) and found that these databases can adequately identify the relevant literature. We will use relevant systematic reviews and meta-analysis to identify additional existing and new literature. We will also search U.S. Food and Drug Administration (FDA), ClinicalTrials.gov, Health Canada, U.K. Medicines and Healthcare Products Regulatory Agency (MHRA), conference proceedings, patient advocate group websites, and medical society websites. Reference mining of relevant publications will be conducted. The search strategy will be peer-reviewed by an independent information specialist. An experienced librarian will conduct the search. All citations identified through the process will be imported to a reference management system (EndNote® Version X9; Thomson Reuters, Philadelphia, PA). In addition, a Supplemental Evidence and Data for Systematic Reviews (SEADS) portal will be available to collect additional study-specific information from industry stakeholders, professional societies, and researchers. A Federal Register Notice will be posted for this review.

For abstract screening, we plan to use a validated Natural Language Processing (NLP) algorithm developed by DistillerSR® (Evidence Partners Incorporated, Ottawa, Canada). Each abstract will be screened by one human reviewer and the NLP technique with constant surveillance of possible misclassified citations for quality control. Consensus for inclusion and conflicts will be advanced for full-text screening. Independent reviewers, working in pairs, will screen the full-text version of eligible references. Discrepancies between the reviewers will be resolved through discussions and consensus. If consensus cannot be reached, a third reviewer will resolve the difference. We will use a web-based systematic review software, DistillerSR (Evidence Partners Incorporated, Ottawa, Canada), to facilitate study selection process.

C. Data Abstraction and Data Management

At the beginning of data abstraction, we will develop a standardized data extraction form to extract study characteristics (e.g., author, year, study design, inclusion and exclusion criteria, patient characteristics (e.g., age, sex, race/ethnicity, country), intervention, comparisons, outcomes, and related items for assessing study quality and applicability). The standardized form will be pilot tested by all study team members using 10 studies. We will iteratively continue testing the form until no additional items or unresolved questions exist. After we finalize the form, reviewers will work independently to extract study details. A second reviewer will review data extraction and resolve conflicts. In case the included studies do not report all necessary information (e.g., methods and results), we will contact authors directly. DistillerSR will also be used to create data extraction forms and facilitate data extraction.

D. Assessment of the Risk of Bias of Individual Studies

We will evaluate the risk of bias of the included RCTs using the Cochrane Collaboration's Risk of Bias 2 tool[16] to assess bias from the randomization process, intended interventions, missing outcome data, outcome measurement, selective reporting, and other sources. For nonrandomized studies, including quasi-experimental studies, controlled before-and-after studies, prospective cohort studies, and nested case-control studies, we will use the Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E) tool.[17] In addition, we will report funding source of the included studies.

E. Data Synthesis

We will qualitatively summarize key features/characteristics (e.g., study populations, design, intervention, outcomes, and conclusions) of the included studies and present in evidence tables for the KQ.

We will determine whether a meta-analysis is appropriate (i.e., more than 2 studies address the same PICOTS and provide point estimates and dispersion measures) to quantitatively summarize study findings based on the similarities of PICOTS presented by the studies. If a meta-analysis is deemed appropriate, we plan to use random-effects models to pool estimates from the included studies. We will evaluate heterogeneity between studies using I^2 indicator.

We will evaluate potential publication bias by evaluating funnel plots symmetry and using statistical tests, such as the Egger linear regression test if the number of studies included in a direct comparison is large ($n \geq 10$).

F. Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

We will grade the strength of the body of evidence (SOE) per the EPC methods guide on assessing SOE.[18] We will grade SOE for selected outcomes, including T2D, gestational diabetes, underweight, overweight, and obesity. These outcomes are chosen because they are either clinically important from a patient's perspective or highly relevant for stakeholders' decision making.

RCTs start as high SOE.[18] The domains to be used for all KQs will be: the methodological limitations of the studies (i.e., risk of bias), precision (based on the size of the body of evidence, number of events, and confidence intervals), directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs surrogates), consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity), and the likelihood of reporting and publication bias.

We will lower the SOE grading when the majority of studies in a particular comparison have high or unclear risk of bias or when sensitivity analyses show substantial difference in estimates derived from high or unclear risk of bias studies versus estimates derived from studies at low risk of bias. If a sufficient body of evidence can be derived from low risk of bias studies, we may exclude high and unclear risk of bias studies and not rate down the SOE. SOE grading will be also lowered when important heterogeneity is identified.

Based on this assessment and the initial study design, we will assign the SOE rating as high, moderate, low, or insufficient evidence to estimate an effect.

High: We are very confident that the estimate of effect lies close to the true effect (i.e., the body of evidence has few or no deficiencies and is judged to be stable).

Moderate: We are moderately confident that the estimate of effect lies close to the true effect (i.e., the body of evidence has some deficiencies and is judged to be likely stable).

Low: We have limited confidence that the estimate of effect lies close to the true effect (i.e., the body of evidence has major or numerous deficiencies and is likely unstable).

Insufficient: We have no evidence, are unable to estimate an effect, or have no confidence in the estimate of effect.

We will produce summary of evidence tables that will provide the following for each comparison and for each outcome: data source, effect size, SOE rating, and rationale for judgments made on each domain of evidence rating.

G. Assessing Applicability

Applicability is limited to the general population.

IV. References

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V. Definition of Terms

AHRQ	Agency for Healthcare Research and Quality
BMI	Body Mass Index
DRI	Dietary Reference Intake
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
GI	Gastrointestinal
HbA_{1C}	Hemoglobin A_{1C}
KQ	Key Questions
MHRA	Medicines and Healthcare Products Regulatory Agency
NAFLD	Nonalcoholic Fatty Liver Disease
NLP	Natural Language Processing
PICOTS	Population, Intervention, Comparator, Outcome, Timing, Setting/Study Design
ROBINS-E	Risk Of Bias In Non-randomized Studies - of Exposure
SEADS	Supplemental Evidence and Data for Systematic Reviews
SOE	Strength of Evidence
T2D	Type 2 Diabetes
TEP	Technical Expert Panel
TOO	Task Order Officer
U.K.	United Kingdom
U.S.	United States

VI. Summary of Protocol Amendments

If the EPC needs to amend the protocol, the EPC will provide the date of each amendment, describe the change, and give the rationale in this section. Changes will not be incorporated into the protocol.

VII. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The Technical Expert Panel (TEP) is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The AHRQ TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

VIII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparing the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

IX. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

X. Role of the Funder

This project was funded under Contract No. 75Q80120D00005 from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed the EPC response to contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by either the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XI. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).